REMARKS

Claim 98 was pending in the application. Claim 98 has been amended in order to more fully and distinctly claim the invention and to correct certain informalities. Support for the claim amendment can be found throughout the specification and claims as originally filed. In particular, support for the amendment to claim 98 can be found in the instant specification at least, for example, at page 12 line 31 through page 14, line 4. No new matter has been added.

Attached hereto is Appendix A, captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**". The attached Appendix includes a marked-up version of the changes made to the specification and claims by current amendmement.

Amendment of claim 98 is not to be construed as an acquiescence to any of the rejections set forth in the instant Office Action and was done solely to expedite prosecution of the instant application. Applicants reserve the right to pursue the claims as originally filed, or similar claims, in this or more patent applications.

I. Objection of Claim 98 Due to Informalities

The Examiner objects to claim 98 because as set forth in Papers Nos. 17 and 22, the pharse "inhibiting responsiveness in an anergic T cell" is considered to be stimulating a response in said T cell since anergic T cells are unresponsive. The Examiner requests that the Applicant provide positive claim language.

Applicants have amended claim 98 to recite "[a] method for inhibiting responsiveness in a T cell comprising contacting said T cell with an agent which prevents or disrupts signaling via the cytokine receptor γ chain such that responsiveness in said T cell is inhibited." Applicants submit that this amendment removes any informalities and therefore respectfully request the Examiner to withdraw this objection.

II. Rejection of Claim 98 under 35 U.S.C. §112, first paragraph

Claim 98 has been rejected inder 35 U.S.C. §112, first paragraph as not being enabling for the full breadth of the term "agent". In particular, the Examiner has rejected claim 98 as not being enabling for either the full breadth of the term "agent" as recited, the reversal of anergy, or the prevention or reversal of anergy *in vivo*. Specifically, the Examiner states on page 3, paragraph 2 and 3 of the instant office action that the specification does not provide sufficient guidance and direction with respect to "agent" as broadly recited. The Examiner further asserts that a person of skill in the art would not be able to make or use an "agent" as encompassed by the full breadth of the claim as currently recited. In further support of the rejection, the Examiner cites Huang (Pharmacol. Therapeutics 2000, 86:201-215) which states that it is a "daunting task faced by the skilled artisan in developing small molecule regulators of protein-protein interactions." Applicants respectfully traverse this rejection.

The specification is replete with examples of agents which can be used to inhibit the responsiveness of a T cell via the cytokine receptor γ chain and methods of making such agents. For example, agents have been identified that can act extracellularly to prevent signaling via the cytokine receptor γ chain. This can be accomplished by utilizing an inhibitory or blocking anti-γ chain antibody (page 3, lines 23-24) or an agent which binds the natural ligand of the γ chain (page 3, line 25). Agents have also been disclosed which can act intracellularly to disrupt signaling via the cytokine receptor γ chain, for example those which inhibit the association of γ chain with JAK 3 kinase (page 3, lines 27-28), those that inhibit phosphorylation of the γ chain (page 3, line 29), those which inhibit the phosphorylation of the JAK3 kinase (page 3, line 30), or both (page 3, lines 29-30). More specifically, the specification discloses that such agents may include anti-γ chain antibodies that bind the cytokine γ receptor such as soluble antibodies or antibody fragments, all of which can be made using techniques known by one with skill in the art (page 13, lines 1-5). The specification also discloses the use of anti-cytokine antibodies which bind the cytokine and prevents and/or inhibit its interaction with its receptor (page 13,

lines 1-13). Finally, the specification also discloses the use of other inhibitory agents which are well known to one with skill in the art such as peptide fragments, modified forms of natural ligands for the receptor γ chain, antisense nucleic acids and other inhibitory agents which block intracellularly by binding to and/or inhibiting the action of the JAK3 kinase (se, *e.g.* page 13, lines 15-26, page 13, lines 27-35, and page 13, line 36 through page 14, line 4).

With regard to the reference cited by the Examiner [Huang (*Pharmacol.Therapeutics* 2000, 86:201-215)], Applicants submit that at the priority date for the present application, the use of fragments, mimietics, and small molecules to substitute for an effect observed for physiological ligands was *not* fraught with uncertainties. There were a number of techniques, such as combinatorial chemistry, high-throughput screening (HTS), computational chemistry and traditional medicinal chemistry that would enable one with skill in the art to make and use an agent as described in the instant specification without undue experimentation. For example, these techniques have been used to develop numerous inhibitors for various tyrosine kinases (see, *e.g.* Al-Obeidi FA, Development of inhibitors for protein tyrosine kinases, 2000, *Oncogene* 19(49):5690-5701), and to easily and quickly quantitate and enrich isolated clones using IgE from allergic patients (see, *e.g.* Crameri R, High-throughput screening: a rapid way to recombinant allergens, 2001, *Allergy* 56:30-34). Moreover, computational modeling and computer-assisted modeling strategies have also been utilized in the analysis and description of antibody interactions, such as determining electrostatics, polarization, hydrophobic interactions, hydration and kinetics (see, *e.g.* Linthicum DS *et al.* Antibody-ligand interactions: computational modeling and correlations with biophysical measurements, 2001, *Comb Chem High Throughput Screen* 4(5):439-449).

Furthermore, Huang states that "in general, interactions between proteins involve large and relatively flat surface areas with many contact sites...which is in contrast to the small, deep active sites in enzyme targets (Introduction, page 202, 1st paragraph, last column)." It is this difference that Huang's belief that protein-protein interactions are a "daunting task," is based.

Applicants wish to point out that the "agents" as described in the instant specification are directed to the common *receptor* γ chain, not a general protein. The common receptor γ chain belongs to a special family of cytokine receptors which contain the WSXWS amino acid motif. These receptors have within them a specific binding site for a particular cytokine, much like a deep pocket enzyme. This level of specificity supports Applicants' position that at the priority date of the present application, techniques such as combinatorial chemistry, high-throughput screening, computational chemistry and traditional medicinal chemistry would yeild specific compounds directed to the common receptor γ chain without undue experimentation.

The Examiner also asserts on page 3, paragraphs 4 and 5 of the instant office action that the specification does not appear to provide sufficient objective evidence that the claimed method can work *in vivo*. The Examiner further asserts that there is insufficient guidance in the specification to direct a person of skill in the art in how to use the agents in a method of inhibiting responsiveness in an anergic T cell once anergy has been established.

Applicants respectfully traverse this rejection First, the specification specifically states that the agents can be used *in vivo* or *ex vivo* in the presence of an antigen (page 3, lines 19-22). Furthermore, the instant specification specifically discloses in Example 6 that allorecognition coupled with complete blockade of common receptor γ chain signaling during primary mixed lymphocyte reaction is necessary to achieve host alloantigen specific anergy (see, *e.g.* page 27, line 10 through page 28, line 38). Specifically, mixed lymphocyte reactions were performed *ex vivo* on isolated peripheral blood mononuclear cells or bone marrow mononuclear cells isolated from individuals using standard techniques known to one with skill in the art. Using these isolated human T cells, Applicants demonstrate that blocking cytokines which signal via the common γ chain is sufficient to induce anergy (see, *e.g.* page 28, lines 20-23). Moreover, these experiments were performed using isolated *human* PBMCs and BMMCs. These cells were used *ex vivo* without any manipulation (*i.e.* not immortalized) making them unique from typical

in vitro assays using established cell lines. These cells behave as they do *in vivo* and allow one with skill in the art to correlate the effects as they would occur *in vivo*.

Furthermore, the specification is replete with examples of therapeutic uses of γ chain inhibitory agents as well as the administration of therapeutic forms of these agents. For example, the specification clearly discloses several uses for these agents, including but not limited to, organ transplantation, graft-versus-host disease, autoimmune diseases such as diabetes mellitus, arthritis, multiple sclerosis, systemic lupus erythematosis, allergy and the induction of antigen-specific anergy for the use as an adjunct to therapies which utilize a potentially immunogenic molecule for therapeutic purposes (see, e.g. page 14, line 28 though page 18, line 5). The specification further discloses that these conditions can be treated by contacting a T cell with a γc inhibitory agent either *in vitro* or *in vivo* using the methods of the invention (page 14, line 31-34). The specification further states that in addition to contacting a T cell with a γc inhibitory agent, the T cell can also be contacted with another agent which inhibits generation of a costimulatory signal in T cells, such as blocking molecules which bind CD28, B7-1, or B7-2 (page 15, lines 9-11). Specific examples disclosed include anti-CD28 Fab fragment, anti-B7-1 or B7-2 blocking antibodies and soluble forms of CTLA4, CD28, B7-1 or B7-2 (page 15, lines 12-15). Similarly, for the treatment of graft-versus-host disease, the specification discloses that donor bone marrow can be treated *in vitro* prior to transplantation with cells from the recipient and a γc inhibitor (page 15, lines 35-36). Alternatively, a γc inhibitory agent can be administered to a transplant recipient together with the transplanted cells to induce alloantigen specific T cell unresponsiveness (pae 15, lines 26-30).

The specification also discloses pharmaceutical compositions of therapeutic forms of γc chain inhibitory agents as well as their administration, including routes and methods of administration, methods for preparing sterile injectable solutions, descriptions of biologically compatible forms of administrable agents and desccriptions of pharmaceutically acceptable carriers (see, e.g. page 18, line 7 through page 20, line 11). From these examples, one with

ordinary skill in the art would be able to make and use a therapeutically derived agent as described in the instant application.

Finally, the Examiner has rejected claim 98 under 35 U.S.C. §112, first paragraph as not providing sufficient guidance to direct a person with skill in the art in how to use the agents in a method of inhibiting responsiveness in an anergic T cell once anergy has been established. Without acquiescing to the Examiner's rejection, Claim 98 has been amended to recite, in pertinant part, a "method for inhibiting responsiveness in a T cell...", thus rendering the rejection moot.

Therefore, for the reasons stated above, Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. §112, first paragraph.

III. Rejection of Claim 98 under 35 U.S.C. §102

Claim 98 has been rejected under 35 U.S.C. §102(b) as being anticipated by Beverly et al (*Int. Immunol.* (1991) 4:661-667) as evidenced by Nelson et al. (*Nature* (1994) 369:333-336). Specifically, the Examiner states that Beverly *et al.* teaches (1) a method to induce anergy in the Th1 mouse T helper cell clone with Concavalin A in the absence of antigen presenting cells *in vitro* to induce anergy and (2) a method to treat anergic cells with IL-2 to induce proliferation and a complete reversal of the anergic state. The Examiner also states that Nelson *et al.* teaches that IL-2 transduces a signal via the cytokine receptor gamma chain.

Applicants traverse and submit that these references fail to teach using an agent that transduces a signal through the cytokine receptor gamma chain so that anergic T cells *do not respond.* It is therefore clear that Beverly *et al.*, in light of Nelson *et al.*, does not anticipate the present invention.

Claim 98 has also been rejected under 35 U.S.C. §102(b) as being anticipated by Boussiotis *et al.* (J. Exp. Med. (1993) 178:1753-1763) as evidenced by Nelson *et al.* The Examiner states that Boussiotis *et al.* teaches the use of an *in vitro* system that evaluates the

capacity of ligands to costimulate alloantigen-induced T cell recognition. Specifically, the Examiner states that Boussiotis *et al.* teaches both B7 and ICAM-1 are equally potent stimulators of T cell proliferation, but only B7 costimulation can prevent the induction of alloantigen-specific anergy. The Examiner specifically relies on Figure 6 which demonstrates that primary stimulation with alloantigen in the presence of IL-2 can prevent the induction of tolerance.

Again, Applicants traverse and assert that claim 98 is directed to *preventing* an anergic T cell from responding to a stimulus (*i.e.* resuming a state of activation). Boussiotis *et al.* fails to teach a method of using an agent that transduces a signal through the cytokine receptor gamma chain so that anergic T cells *do not respond* (i.e. remain anergic). Therefore, it is clear that Boussiotis *et al.*, in light of Nelson *et al.*, does not anticipate the present invention.

Claim 98 is also rejected under 35 U.S.C. §102(e) as being anticipated by de Boer *et al.* (US 5,747,034) as evidenced by Nelson *et al.* The Examiner states that de Boer *et al.* teaches a method to induce anergy by utilizing antibodies to B7-1 and an immunosuppressant such as cyclosporin A. The Examiner specifically relies on Example 15, columns 30-32 which describe using B7 in combination with cyclosporin A to maintain anergy and preventing the induction of anergy by adding IL-2.

Applicants traverse and submit that de Boer *et al.* teaches methods to *induce* anergy but fails to teach a method of using an agent that transduces a signal through the cytokine receptor gamma chain so that anergic T cells *do not respond* (i.e. remain anergic). Therefore, it is clear that de Boer *et al.*, in light of Nelson *et al.*, does not anticipate the present invention.

In summary, Applicants submit that claim 98 as defined herein is patentable over the cited references. Accordingly, reconsideration and withdrawal of the 35 U.S.C. §102(b) and (e) rejections are respecfully requested.

IV. Rejection of Claim 98 under U.S.C. §103(a)

Claim 98 has been rejected under 35 U.S.C. §103(a) as being unpatentable over either Beverly *et al.* or Boussiotis *et al.* or de Boer *et al.* in view of Nelson *et al.* The Examiner's rejection is based on the assumption that claim 98 is directed to *stimulating a response* in a T cell since anergic T cells are unresponsive.

Applicants traverse. Claim 98 as amended is directed to *preventing* an anergic T cell from responding to a stimulus. Therefore, the invention is not obviated by these references and Applicants respectfully request that the Examiner remove this rejection.

V. Statement regarding Double Patenting

The Examiner states that the language of instant claim 98 of "inhibiting responsiveness in an anergic T cell" is "considered to be stimulating a response in said T cells [sp] since anergic T cells are unresponsive". The Examiner also notes that pending claim 98 of USSN 08/270,152 recites "stimulating responsiveness in an anergic T cell" wherein the agent is an antibody to the common γ chain. Therefore, the Examiner states that because there is some uncertainty with respect to the language of claim 98 of USSN 08/270,152 as well as instant claim 98, Applicant is requested to confirm that these claims do not represent overlapping subject matter with regards to the end effect on the anergic T cell.

Claim 98 as amended does not represent overlapping subject matter with regards to the end effect on an anergic T cell, as claimed in claim 98 of USSN 08/270,152. Specifically, claim 98 as amended is directed to the inhibition of responsiveness in an anergic T cell, comprising contacting said T cell with an agent which prevents or disrupts signaling via the cytokine receptor γ chain. Alternatively, pending claim 98 of USSN 08/270,152 is directed to stimulating responsiveness in an anergic T cell, wherein the agent is an antibody to the common γ chain. Therefore, the nonstatutory double patenting rejection should be withdrawn.

[redacted] If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at (617) 227-7400.

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October 17, 2001
Date

DeAnn F. Smith Reg. No. 36,683

Respectfully submitted,

LAHIVE & COCKFIELD, LLP

DeAnn F. Smith
Registration No. 36,683
Attorney for Applicants

October 17, 2001

APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

98. A method for inhibiting responsiveness in an anergic T cell, comprising contacting said T cell with an agent which ~~transduces a signal~~ prevents or disrupts signaling via the cytokine receptor γ chain such that ~~T cell responsiveness is inhibited~~ responsiveness in said T cell is inhibited.